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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,096	02/04/2002	Om Reddy Gaddam	U 013840-5	4298

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EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,096	GADDAM ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7,9 and 11-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,3,5,7,9,11-19 and 64* is/are allowed.

6)☒ Claim(s) *20-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 8/15/03. Applicant has amended claims 1, 3, and 11. Applicants have cancelled claims 2, 4, 6, 8, 10, and 65. There are fifty-nine claims pending and fifty-nine under consideration. Claims 1, 2, and 11 are compound claims. Claims 12-23 are composition claims. Claims 24-63 are use claims. Claims 3, 5, 7, 9, and 64 are synthesis claims. This is the second action on the merits. The application concerns some salts of phenoxazine and phenothiazine compounds, compositions, synthesis, and uses thereof.

Response to Amendment

2. Applicants' amendment to the title and specification overcome the formal objections made in points #2 and #3 in the previous office action. Applicants' deletion of derivatives and analogs from claims 1 and 3 overcomes the indefiniteness rejection made in point #4 and #5. Applicants specification of the specific salts "M" claimed overcomes the anticipation rejections over Lohray ('453), Lohray (WO 99/19313 A1), Lohray ('961), and Lohray (WO 00/50414A1), made in points #8-#11. None of the specific salts presently claimed are taught or suggested by these references. This also overcomes the rejection under 35 USC 102(f) made in point #12, since the same subject matter is no longer being claimed. Additionally, the double patenting rejections over the same art made in points #13-#16 are overcome by these same amendments. Applicants' preliminary amendment

to Application 10/007,109, requiring that L_1 be a leaving group and not the presently claimed phenoxypropanoic acid distances the claims of that application from the present compounds claims. Thus, the double patenting rejection made in point #17 is withdrawn.

Claim Rejections - 35 USC § 112

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 30-35 and 52-55 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 30-35 and 52-55 recites the limitation "dementia", "cancer", and "inflammation" in lines 7 and 9. There is no antecedent basis for this limitation in parent claim 24, which recites "diseases in which insulin resistance is the underlying pathophysiological mechanism". Applicants have not asserted and it is not art recognized that the three rejected diseases are so mechanistically related.

Applicants argue that a relationship was shown between inflammation and insulin resistance by the clinical observation of Ishibashi that the drug pioglitazone reduces the lesions, produced as a side-effect, of L-NAME treatment. This is unpersuasive for three reasons. First of all, this says nothing about cancer and dementia. Secondly, how does this isolated observation establish the cause and

effect relationship implied by Applicants claim language? Since the lesions are, by definition, caused by administration of the drug L-NAME, how can insulin resistance be the underlying cause? Pioglitazone is a PPARγ agonist used experimentally to treat insulin resistance. Might not the lesion reversal be incidental to the insulin resistance? If PPARγ receptors are mechanism of both insulin receptors and L-NAME induced lesion, then how is one the cause of the other? Thirdly, lesions, produced as a side-effect of L-NAME treatment, hardly constitute all inflammations, which have a bewildering array of causes.

4. Claims 20-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating type II diabetes, insulin resistance, and hypercholesteremia, does not reasonably provide enablement for treating the multitude of unrelated diseases embraced. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that

art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Determining if any particular claimed compound would treat any particular PPARα or PPARγ related disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) The direction concerning treating diseases is found in paragraph 104, spanning pages 17 to 18, which merely states Applicants' intention to do so. Applicants describe formulations in paragraphs 106 to 112, spanning pages 18 to 21. Two prophetic examples of the formulations required to practice Applicants intended therapies are reported. Doses required to practice their invention are described in paragraph 113, page 21. A 10,000-fold range of doses is recommended. The thiazolidedione compounds troglitazone, rosiglitazone, and pioglitazone are the only PPARγ antagonists ever used to treat any human disease. These compounds are structurally unrelated to those of Applicants. No PPARα agonist has ever shown clinical efficacy in human disease therapy. How then is the skilled physician to know what dose of Applicants' compounds to use

for each of these dozen different diseases? There are two PPARα or PPARγ receptor binding *in vitro* assays described in paragraphs 192-213, spanning pages 36-42. There is data for six of Applicants' compounds. It is unclear if these two assays are correlated to clinical efficacy for any disease treatment. It is also not possible to conclude if Applicants compounds are agonists or antagonists at these receptor sites. Antagonists, would of course exacerbate, the pathological conditions that Applicants intended to treat. There is an *in vivo* cholesterol-lowering assay in the rat reported. Only one of Applicants' compounds has been tested in this assay. There is a prophetic HMGCo enzyme assay and there are three prophetic diabetes, cholesterol lowering in the mouse, and obesity assays also described. None of Applicants compounds appear to have been tested for these therapeutic indications.

c) There is no working example of treatment of any disease in man. There is one compound tested for hypercholesteremia in the rat. d) The nature of the invention is clinical treatment of disease with PPARα or PPARγ antagonists, which involves physiological activity. e) The state of the clinical arts in PPARα or PPARγ related diseases is provided by Cobb (Ann. Reports Med. Chem.) that antidiabeteic efficacy has been correlated to affinity to the PPARγ binding site, in the first paragraph, page 216. Sapone (Pharmacogenetics) reports that mice lacking any PPARα receptors develop normally. In his abstract he says that "[t]he

biological significance of these novel PPARalpha alleles remains to be established".

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1 as well as the dozens of claimed diseases. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants cite a number of research articles in support of their assertion to treatment of a number of diseases. None of these contain any clinical evidence but offer only speculation and direction for future research. None of these establish the correlation between the screening assays used by the Applicants and treatment efficacy required by the case law. Substantiation of use and scope is required

when the use is "speculative", "sufficiently unusual", or not provided in the specification, *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

Allowable Subject Matter

5. Claims 1, 3, 5, 7, 9, 11-19, and 64 are allowed.

Conclusion

6. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK